the amended claims is found throughout the specification and claims as originally filed, and in the Figures.

The present invention relates to a method for vaccinating a mammal against an antigen by administering to the mammal a vaccine composition of the invention which comprises a cytokine-coated cell, wherein the cytokine coated cell comprises the antigen of interest, and which is in mixture with an exogenous cytokine. In one embodiment, the exogenous cytokine is a fusion protein comprising a cytokine fused to a heterologous cell membrane binding moiety.

Formal Matters

Priority

The Examiner notes that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date. Applicants submit that the specification has been amended to include a specific reference to the prior application to which the present application claims priority in the first sentence of the specification.

Rejection of Claims 1-8, 13-14, 17-20, and 22-25 Under 35 U.S.C. 112, second paragraph

The Examiner states that the claims are rejected as being incomplete for omitting an essential resolution step that reads on the preamble of the method claims.

Solely for the purpose of expediting the prosecution of the present application, Applicants have amended independent claims 1, 2, and 13 to recite ", and wherein said animal is vaccinated against said antigen", thus expressly reciting a resolution of the claimed method. Applicants accordingly request that the rejection be reconsidered and withdrawn.

Rejection of claims 1-8, 13-14, 17-20, and 22-25 Under 35 U.S.C. 112, first paragraph

The Examiner has rejected claims 1-8, 13-14, 17-20 and 22-25 under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner asserts that there is no teaching of the amount of GM-CSF which adheres to the cells, or how much is necessary to be effective in a method of vaccinating a mammal to the target antigen. The Examiner further asserts that

because the actual amount of cytokine on the recited cytokine coated cells that would be administered in the recited method is not disclosed, and because the local effective concentration of cytokine that would be available after administration of the recited cytokine coated cells has not been taught, and because the concentration of any cytokine that would be effective in a vaccine against any antigen has not been taught, it would require undue experimentation for one of skill in the art to practice the method. Applicants respectfully disagree.

The claims of the present invention relate to a method of vaccinating a mammal to a selected antigen comprising administering to a mammal a cytokine coated cell comprising the antigen and an exogenous cytokine. As the Examiner acknowledges, the specification teaches that an exogenous cytokine refers to a cytokine which is introduced form or produced outside the cell. That is, the vaccine composition comprises a cell having the antigen of interest, and which is mixed with an exogenous cytokine. Accordingly, in order for one of skill in the art to practice the present invention, the specification must teach the amount of exogenous cytokine which is to be mixed with the cell to generate the claimed vaccine. Contrary to the Examiner's assertion, one of skill in the art need not know the local concentration of cytokine, or the actual amount of cytokine on the cytokine-coated cells; the invention may be practiced as claimed without knowing the information which the Examiner asserts is lacking from the specification.

The specification teaches on page 78 that a cytokine-coated cell preparation will consist of about 10^4 to 10^8 cells mixed with 1-100 μg/ml cytokine. The specification teaches further at page 106 that a suitable dose range for the administration of the active ingredient per vaccination is from about 0.1 to 1000 μg. Thus, the specification teaches the amount of cytokine which is to be mixed with a cell comprising the target antigen for use in the claimed method.

Applicants also submit the Declaration under 37 C.F.R. 1.132 of Dr. Andrew Segal which provides data demonstrating the ability of a cytokine coated cell as described in the present invention to act as a vaccine against tumor production in a mouse model. The Declaration teaches that CMS-5 fibrosarcoma cells bearing a target antigen (endogenous tumor antigen) were mixed with engineered GM-CSF, wherein the engineered GM-CSF is a fusion protein comprising GM-CSF fused to glycosylphosphatidylinositol at a concentration of 1 μg GPI-GM-CSF per 10^6 cells. The cells were incubated for three hours and subsequently administered to 8-

10 week old Balb/c mice. The mice were vaccinated in the left inguinal fold with 10^6 cells in 0.25 ml. That is, the animals are vaccinated with a total of 4 μg GPI-GM-CSF/ml. Vaccination with 4 μg cytokine is at the lower end of the concentration range taught in the present specification (as noted above, the specification teaches that animals may be vaccinated with between 1 – 100 μg cytokine/ml (page 78), and alternatively 0.1 – 1000 μg cytokine (page 106). The Declaration teaches that vaccination with cytokine coated CMS-5 cells protected the mice from challenge with wild-type CMS-5 cells (see Exhibit A). The data indicates that both a vaccine composition which had been washed prior to administration to remove any GPI-GM-CSF which had not intercalated into the cell membrane, or a vaccine composition which had not been washed prior to administration were able to vaccinate mice against tumor cell challenge. Regardless of whether the vaccine composition is washed or unwashed, the data provided in the accompanying declaration clearly indicates that a vaccine composition which contains an amount of cytokine within the range of amounts taught in the present specification, is effective in protecting a test animal against tumor cell challenge.

The Examiner also asserts that Mahvi et al (human Gene Therapy, 1997 8:875) teach that GM-CSF induces macrophage-associated tumoricidal activity, but that routine expression of transfected GM-CSF does not necessarily validate this treatment as a vaccination strategy. The Examiner asserts further that Mahvi et al teach that in a murine neuroblastoma system the *in vitro* expression of GM-CSF of 10 ng/10 million cells/24 hours is necessary to protect animals form subsequent tumor challenge. Applicants respectfully submit that the teachings of Mahvi et al do not apply to the present invention. The claims of the present invention relate to a cytokine-coated cell comprising an exogenous cytokine, that is, a cytokine which is introduced from or produced outside the cell (see page 10 of the specification). Thus, the teachings of Mahvi et al with respect to transfected, secreted GM-CSF do not bear on the present claims. Moreover, the concentration of secreted GM-CSF taught by Mahvi et al which is needed to protect animals from subsequent tumor challenge is not relevant to the amount of cytokine taught in the specification (and in the Declaration of Dr. Segal) which is to be mixed with the cells of the invention to effectively vaccinate an animal.

Applicants accordingly submit that the present invention is enabled for the full scope of the instant claims. Applicants therefore request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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Marked-Up Version of Amendment

1. A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell comprising said selected antigen, wherein said cytokine of said cytokine-coated cell is exogenous to said cell, and wherein said mammal is vaccinated to said selected antigen.

2. A method of vaccinating a mammal to a selected antigen, the method comprising

administering to a mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine-coated cell comprises said selected antigen and is admixed with an engineered cytokine, and wherein said mammal is vaccinated to said selected antigen.

13. A method of vaccinating a mammal to a selected antigen, the method comprising administering to the mammal a vaccine composition comprising a cytokine-coated cell, , wherein said cytokine of said cytokine-coated cell is exogenous to said cell, wherein said cytokine is a ligand for the GM-CSF receptor, and wherein said mammal is vaccinated to said selected antigen.